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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/804,014	Applicant(s) LI ET AL.	
	Examiner Daniel M Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-14,30,33 and 44-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-14,30,33 and 44-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 12 March 2001 claiming benefit of U.S. Provisional Patent Application Nos. 60/188,316 filed 10 March 2000, 60/188,277 filed 10 March 2000, 60/189,139 filed 14 March 2000, 60/189,140 filed 14 March 2000, 60/190,401 filed 17 March 2000, and 60/190,231 17 March 2000. Claims 1-43 were subject to a restriction requirement in Paper No. 14 mailed 20 September 2002. Claims 1-4, 15-29, 31, 32 and 34-43 were canceled, claims 5, 9 and 10 were amended and claims 44-52 were added in the "Supplemental Preliminary Amendment" filed 21 January 2003 (Paper No. 17).

Election/Restrictions

Applicant has constructively elected the subject matter of Group XII, directed to an isolated nucleic acid molecule encoding the polypeptide sequence set forth as SEQ ID NO:8 and variants thereof, by the amendments to the claims in Paper No. 17. Because applicant did not distinctly and specifically point out errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5-14, 30, 33 and 44-52 are pending and under consideration herein.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The elected invention is disclosed in U.S. Provisional Application 60/188,277 only. Therefore, a the priority date of 10 March 2000 will be used to determine patentability of the claimed invention over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are directed to an isolated nucleic acid molecule comprising nucleotides 382-631 or 970-1525 of SEQ ID NO:7, and pharmaceutical compositions and kits comprising said nucleic acid molecules. There is no support for nucleic acid molecules limited to comprising nucleotides 382-631 or 970-1525 of SEQ ID NO:7 in the specification or claims as filed.

Claims 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims encompass a genus nucleic acids encoding any and all variants of the polypeptide set forth as SEQ ID NO:8 which are translated from a naturally occurring allelic variants or single nucleotide mutations in the gene encoding SEQ ID NO:8. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). However, the instant specification does not provide a single example of a polypeptide having the claim limitations, but merely teaches how variants of the gene encoding SEQ ID NO:8 might be identified. An adequate written description of a nucleic acid molecule requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the nucleic acid itself. It is not sufficient to define nucleic acid solely by its

principal biological property (i.e., it is naturally occurring and encodes a variant of the polypeptide sequence set forth as SEQ ID NO:8) as in the instant case, is simply a wish to know the identity of any nucleic acid with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all nucleic acids that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of nucleic acids encoding variants of the polypeptide set forth as SEQ ID NO:8 which are translated from a naturally occurring allelic variants or single nucleotide mutations in the gene encoding SEQ ID NO:8. Therefore, only the described nucleic acids encoding the sequence set forth as SEQ ID NO:8 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 5, 9-14, 30 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide sequence of SEQ ID NO:8, does not reasonably provide

enablement for any and all nucleic acid molecules encoding polypeptides comprising variants or fragments of the amino acid sequence set forth as SEQ ID NO:8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and breadth of the claims: The claims are directed to an isolated nucleic acid molecule encoding a polypeptide comprising an amino acid sequence having at least 85% sequence identity with the sequence set forth as SEQ ID NO:8, fragments thereof, and a vector, cell, pharmaceutical composition and kit comprising said nucleic acid molecule. The claims thus encompass a vast genus of any nucleic acid molecule encoding a polypeptide wherein any amino acid in the polypeptide sequence of SEQ ID NO:8 is replaced with any of the other 19 naturally occurring amino acids, or presumably any non-naturally occurring amino acid, so long as the polypeptide sequence retains 85% sequence identity with SEQ ID NO:8.

State of the prior art and level of predictability in the art: The prior art generally teaches that nucleic acid molecules can be used for the purpose of heterologous expression, to suppress

expression by antisense knockout technologies, or as probes for identical or homologous nucleic acid sequences. However, the utility of these methods is highly dependent upon the particulars of the nucleic acid sequence because the functional properties of the expressed or inhibited protein or nucleic acid, or the identity nucleic acid identified by hybridization is dictated by the nucleotide sequence.

The art further teaches that the effect of varying amino acid sequence on the function of a polypeptide is highly unpredictable. For example, Richards (1997) *Cell Mol. Life Sci.* 53:790-802 teaches, "[i]n terms of structural alterations and thermostability, responses to genetic mutations are context dependent and remain difficult to predict with any confidence" (abstract, column 1). Thus, Richards teaches that the effect of mutation on protein stability, a prerequisite for biological function, is unpredictable. Richards also teaches that even limited amino acid modifications can have dramatic effects on protein structure and function. In the second column on page 791, Richards cites the example of influenza virus hemagglutinin protein, wherein alterations in the ionization state of just a few ionizable groups dramatically alters the biological behavior of the molecule. Citing a published study of done on the gene V protein, Richards teaches that, in spite of only limited modification at two amino acid positions, "[t]he effects on the overall stability of the protein were remarkably variable" (page 794, column 1). In the paragraph bridging pages 796 and 797, Richards teaches,"[i]n single site mutants, the structural changes are generally greatest near the site of mutation, and moving away, decrease radially in all directions. *Even the small changes are so complex that the linkage relations do not allow assignments of the energetic changes to unique parts of the altered residue and its immediate contacts*" (emphasis added) and "[t]here is no convincing explanation yet of how the changes in

binding can produce a major movement over such a distance." Finally, in the first full paragraph in the second column on page 793, Richards teaches, "[a]lmost all mutations are accompanied by some conformational change, making prediction of the effects on stability difficult. *In most cases mutations lead to lowering of the stability.*" (emphasis added). Thus, Richards teaches that small changes in the primary structure of a protein frequently have dramatic effects on the higher order structure and function of the protein, and that these effects are highly unpredictable. Given these teachings, the skilled artisan would understand that most of the polypeptides encompassed by the genus of all polypeptides having at least 85% identity with the polypeptide set forth as SEQ ID NO:8 would be less stable, and would likely not have the function of a polypeptide comprising SEQ ID NO:8.

Therefore, the vast majority of the nucleic acid molecules claimed in the instant application would not encode a functional polypeptide and thus would have no known function. The prior art must obviously be silent regarding how to apply a nucleic acid having no known function to solving a real world problem. The art does not generally teach a real world utility for all nucleic acid sequences because the utility of each nucleic acid is linked to its unique function. As it is not yet possible to predict function based solely on the structure of a nucleic acid, function can only be discovered by empirical experimentation.

Amount of direction provided by the inventor and existence of working examples: The specification (beginning at page 16 and continued through page 21) teaches that the polypeptide having the sequence of SEQ ID NO:8 shares significant homology with a family of voltage-gated potassium channels and thus would credibly have the function of a voltage-gated potassium channel. The specification teaches that nucleic acids encoding the polypeptide set forth as SEQ

ID NO:8 can be used to produce the protein, to raise antibodies, to detect mRNA, to detect genetic lesions, to modulate activity of the protein and to screen for drugs or compounds. However, clearly nucleic acid molecules encoding proteins that do not have the structure or function of the protein comprising SEQ ID NO:8 could not be used according to the teachings of the specification. That is, the skilled artisan would not know how to screen for drugs or compounds that modulate the function of a protein if the function of the protein is unknown. Likewise, most antibodies raised against proteins of modified structure or the nucleic acid sequences encompassed by the claims that do not encode SEQ ID NO:8 would not detect a protein or nucleic acid having any known function, and therefore would not provide useful information to the skilled artisan. Thus, the instant disclosure teaches the skilled artisan how to use only polynucleotides encoding a polypeptide having the function of a voltage-gated potassium channel. Beyond that, the specification is silent with regard to how the skilled artisan might use the vast majority of nucleic acids encompassed by the claims, which do not have the function of a voltage-gated potassium channel.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the instant claims encompass a large genus of nucleic acid molecules of disparate structure, most of which would have no known function. Although the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled (*Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; hereinafter *Atlas*), *Atlas* also provides, "[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be

invalid" (page 414). In the instant case, the claims encompass an enormous number of embodiments, the vast majority of which would be inoperative. Furthermore, the art teaches that it is not possible to predict which embodiments would be operative or inoperative without engaging in empirical experimentation to test each and every embodiment. Therefore, determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is normally required in the art. Therefore, the disclosure is enabling only for a nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide sequence of SEQ ID NO:8.

Claims 30, 33, 45, 46, 48, 49, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Breadth of the claims: The claims are limited to a *pharmaceutical* composition comprising the claimed nucleic acid molecules. Thus, the claims clearly encompass a composition to be used in the treatment of a disease. With regard to treatment, the disclosure specifically provides that the nucleic acids of the instant invention can be used to treat Episodic Ataxia type 1, Long QT Syndrome 1 and 2, Benign Neonatal Epilepsy, Jervell and Lange-Neilson Syndrome, autosomal dominant deafness, non-insulin dependent diabetes mellitus, CNS disorders, arrhythmia, seizure, asthma or hypertension (page 22). Thus, the enabling disclosure must teach the skilled artisan how to use the claimed invention to treat these conditions without engaging in experimentation beyond what would generally be considered routine in the art.

Further, as the only mode of therapy contemplated for pharmaceutical compositions comprising nucleic acid molecules is gene therapy (page 92 paragraph 1, and beginning the paragraph bridging pages 115 and 116 and continued through the first paragraph on page 116), the disclosure must be enabling for the treatment of the above conditions using a gene therapy approach.

State of the prior art and level of predictability in the art: At the time of filing, gene therapy utilizing the administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states, "[t]he Achilles heel of gene therapy is gene delivery...", and, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a

therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125). Thus, the art clearly establishes that, at the time of filing, expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art was very low.

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). With regard to treatment of the specific set of conditions set forth in the instant application using the claimed compositions, the art is silent. Therefore, the skilled artisan must rely solely on the instant disclosure to teach how to overcome the specific technical hurdles that Rubanyi teaches will be encountered in development of gene therapy for Episodic Ataxia type 1,

Long QT Syndrome 1 and 2, Benign Neonatal Epilepsy, Jervell and Lange-Neilson Syndrome, autosomal dominant deafness, non-insulin dependent diabetes mellitus, CNS disorders, arrhythmia, seizure, asthma or hypertension using the claimed composition.

Amount of direction provided by the inventor existence of working examples: The teachings of the specification with regard to using a pharmaceutical composition comprising the claimed nucleic acids amounts to merely a general statement that the compositions can be used to treat various conditions and a recitation of molecular cloning and protein expression techniques that are common in the art. There is nothing in the disclosure that would enable the skilled artisan to overcome the well established barriers to effective gene therapy of any condition, or to overcome the as yet unknown barriers to effective gene therapy of any one of the many conditions listed in the specification without engaging in trial and error experimentation to overcome each of these barriers.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods of the instant claims 11 and 12 without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification

and prior art would not enable the ordinary skilled artisan to use the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-14, 30 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are first indefinite in being directed to a nucleic acid molecule encoding a "mature form" of the amino acid sequence given in SEQ ID NO:8. The specification does not set forth metes and bounds for a "mature form" of SEQ ID NO:8 or the NOV4 polypeptide. Therefore it is unclear what is being claimed.

Next, claim 5, and claims 6-14, 30 and 33 as they depend therefrom, are indefinite in being directed to a nucleic acid molecule encoding a polypeptide wherein that nucleic acid molecule is the complement of a nucleic acid molecule encoding a claimed polypeptide (i.e., claim 5, part (f)). It is extremely unlikely that the complement of a nucleic acid molecule encoding any given polypeptide would encode a useful polypeptide.

Claims 11-14 are also indefinite because it is not possible to ascertain what is being claimed in claim 11. It appears that the claim sets forth a Markush group of nucleotide sequences from which any nucleotide specified in the coding sequence of the chosen nucleotide sequence is changed. However, it is not clear how the species in the Markush group are related. It would

appear that the phrase "to a different nucleotide provided that no more than 15% of the nucleotides in the chosen sequence are so changed" is misplaced in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5, 9, 10, 44, 47 and 50 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by NCBI online, Accession No. AC008687 (hereinafter AC008687; made of record in the IDS filed 30 August 2001).

The claims are directed to a nucleic acid molecule comprising a nucleic acid sequence encoding the polypeptide set forth as SEQ ID NO:8 (claim 5), or wherein the nucleotide sequence encoding said polypeptide is the instant SEQ ID NO:7 (claim 9), or hybridizes under stringent conditions to a nucleic acid comprising SEQ ID NO:7 (claim 10), or comprises nucleotides 38-1717 of SEQ ID NO:7 (claim 44), or comprises nucleotides 382-631 of SEQ ID NO:7 (claim 47), or comprises nucleotides 970-1525 of SEQ ID NO:7 (claim 50). As AC008687 discloses a nucleic acid comprising a sequence that is 100% identical to SEQ ID NO:7 over its entire length (see the attached sequence alignment), the disclosure clearly anticipates the claimed subject matter.

Claims 5, 7 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalman *et al.* (1998) *J. Biol. Chem.* 273:5851-5857 (made of record in the IDS filed 30 August 2001).

Kalman *et al.* teaches a nucleic acid comprising a nucleic acid sequence encoding a variant of SEQ ID NO:8 having 85% identity with the sequence set forth as SEQ ID NO:8 and fragments thereof according to claim 5 and 11 (see attached sequence alignment), wherein the nucleic acid sequence encodes a naturally occurring variant of SEQ ID NO:8 according to claim 7. In the fourth full paragraph on page 5852 Kalman *et al.* further teaches an expression construct for electrophysiological studies which the skilled artisan would understand to comprise a vector comprising the nucleic acid operably linked to a promoter according to claims 12 and 13, and which would be propagated in a cell according to claim 14. The nucleic acid molecule, vector and host cell taught by Kalman *et al.* are the same as those claimed in the instant application; therefore the claims are anticipated by Kalman *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 31, 2003

JAMES KETTER
PRIMARY EXAMINER